REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 1, 3, 16, 22, 23, 27, 28, and 30-32 are currently pending in this application. Claims 3, 16, 22 and 23 have been allowed. Claims 1 and 30 are objected to by the examiner. Claims 27, 28, 31 and 32 remain at issue.

In paragraphs 1 and 2 of the official action, the examiner objected to claims 1 and 30 for the recitation of the term "dapA promotor," and suggested replacing this term with "dapA promoter." In addition, the examiner objected to the phrase "wherein said overexpression...gives a pyruvate carboxylase activity or dihydrodipicolinate synthase activity above the level..." because the term "gives a" is unclear. The applicants have adopted the examiner's suggestions for amending claims 1 and 30 in order to clarify terms and correct an inadvertent spelling error. These amendments are not related to reasons of patentability.

In paragraph 16 of the official action, the examiner objected to claim 30 under 37 C.F.R. §1.75 as allegedly being a substantial duplicate of claim 3. In order to expedite prosecution and without prejudice to the applicants' right to seek broader claims in a continuing application, claim 3 has been canceled without prejudice thereby obviating the objection of this claim.

The applicants request entry of the foregoing amendment as entry will overcome the outstanding rejections and/or place the claims in better form for appeal. The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Under 35 U.S.C. §112, Second Paragraph, Indefiniteness

In paragraphs 4 and 5 of the official action, the examiner rejected claims 31 and 32 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter the applicants regard as the

invention. Specifically, the examiner alleged the term "overexpressed" is a relative term and the specification allegedly fails to define this term.

Amended claim 31 is directed to a bacterium of claim 30, further comprising an overexpressed *lys*C gene of *Corynebacterium glutamicum* encoding aspartate kinase wherein said gene is expressed at a level that is higher than its expression level in wild type *Corynebacterium glutamicum* and overexpression of said gene is achieved by increasing the copy number of said gene. Support for amended claim 30 can be found throughout the specification as originally filed, *e.g.*, on page 11, line 28 to page 12, line 23.

Claim 32 is dependent from claim 31 (*e.g.*, aspartate kinase) and therefore is clearly defined by the specification. In view of the foregoing amendments and remarks, the applicants respectfully submit that the rejection of claims 31 and 32 pursuant to 35 U.S.C. §112, second paragraph, for allegedly being indefinite, is overcome and should be withdrawn.

Rejection Under 35 U.S.C. §112, First Paragraph

Written Description

In paragraph 7 of the official action, the examiner rejected claims 27, 28, 31, and 32 under 35 U.S.C. §112, first paragraph, for allegedly lacking proper written descriptive support.

The examiner alleged that although the claims as amended are now limited to *C. glutamicum lys*C genes, the claims are still directed to bacterium wherein the *C. glutamicum lys*C gene, or mutant thereof, is overexpressed by any means and not just by increasing the gene copy number. The examiner asserted that the specification fails to disclose which mutations in the promoter, regulatory region or the ribosome binding site of the recited genes will result in increased expression of said genes. The examiner further alleged that while the specification discloses that a mutant *C. glutamicum lys*C gene encoding an aspartate kinase which is resistant to inhibition by lysine and/or threonine is disclosed in EP-B-0-387 527, the specification fails to disclose which is the structure of said mutant *lys*C gene or the mutant aspartate kinase encoded by it. Finally, the examiner alleged that while the claims encompass a genus of mutant *C. glutamicum lys*C genes, there is no disclosure of other structural modifications in the *C. glutamicum lys*C gene which would result in the corresponding

apparatus kinase to be resistant to inhibition by lysine and/or threonine have been disclosed. In view of the foregoing remarks, the applicants respectfully traverse the written description rejection.

The applicants submit claims 27 and 31 are directed to the end result (*i.e.* overexpression) of either enhancing promoter activity, increasing copy number of a gene via an expression vector, or altering the regulatory region of ribosomal bindin to increase translation efficiency of the *lys*C gene. The specification provides in full, clear, concise, and exact terms, not only methods for increasing productivity of an amplified *lys*C allele (e.g., pg. 2, line 16-19 ref. EP-B-0387527; pg 3, lines 18-24 ref. DE-A-3943117 and EP-A-O-841395)(see also lines 31-35 of pg 3), but also methods for creating inducible *lys*C promoters, prolonging the life of the *lys*C mRNA to improve the expression, or enhancing the activity of the enzyme protein encoded by the *lys*C gene (pg. 7, line 26- pg. 8, line 23). One of skill in the art may use the teachings of the specification to isolate, clone and manipulate the sequence of the *lys*C gene (see pg. 11, line 28 to pg. 12, line 6). The teachings of the specification also provide one of skill in the art means of incorporating the *lys*C gene and its regulatory regions into a suitable plasmid vectors and host strains, and how to cultivate them (see page 12, line 7 to pg. 13, line 15). Methods of mutagenesis for purposes of enhancing promoter activity or increasing mRNA stability by enhancing ribosomal binding sites is taught on page 8, lines 27-31 and Example 15. In fact, Examples 15-19 teach the methods for mutating a promoter of a C. *glutamicum* gene (*i.e.*, the *dap*A gene), selecting and cloning these enhanced promoters, and characterizing these enhanced genetic isolates using the L-lysine assays. Whether the specific residues or nucleotides required are identified or not for the *lys*C gene, one of skill can still use the teachings of the specification in order to apply the screening methods and assays outlined in the specification to identify stronger promoters and/or ribosomal binding sites in order to overexpress the lysC gene product. Accordingly, the applicants respectfully submit sufficient written descriptive support is provided for one of skill in the art to understand overexpression of the lysC gene refers to copy number, strong promoters, or means for stabilizing mRNA.

Nevertheless, in order to expedite prosecution and without prejudice to the applicants right to seek broader claims in a continuing application, claims 27 and 31 have been amended thereby obviating the rejection of these claims.

Specifically, amended claim 27 is directed to the bacterium of claim 1 further comprising an overexpressed lysC gene of Corynebacterium glutamicum encoding aspartate kinase, wherein said gene is expressed at a level that is higher than its expression level in wild type Corynebacterium glutamicum by increasing the copy number of said gene.

As discussed above, amended claim 31 is directed to a bacterium of claim 30, further comprising an overexpressed *lys*C gene of *Corynebacterium glutamicum* encoding aspartate kinase wherein said gene is expressed at a level that is higher than its expression level in wild type *Corynebacterium glutamicum* and overexpression of said gene is achieved by increasing the copy number of said gene. Support for amended claims 27 and 31 can be found throughout the specification, for example, on page 11, line 28 to page 12, line 23.

Claims 28 and 31 depend from either claim 27 or 31 and therefore, are also properly described in the specification. In view of the foregoing amendments and remarks, the applicants respectfully submit that the rejection of claims 27, 28, 31, and 32 pursuant to 35 U.S.C. §112, first paragraph, for allegedly lacking written descriptive support, has been overcome and should be withdrawn.

Enablement

In paragraph 10 of the official action, the examiner rejected claims 27-28 and 31-32 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement. Specifically, the examiner alleged that the specification, while being enabling for a *C. glutamicum* cell wherein the wild type *C. glutamicum pyc* gene, wild type *C. glutamicum dap*A gene, wild type *C. glutamicum lys*E gene, and the wild type *C. glutamicum lys*C gene are overexpressed by increasing the copy number of such genes, the specification does not reasonably provide enablement for a *C. glutamicum* cell further capable of overexpressing the *C. glutamium lys*C gene by any means or overexpressing a *C. glutamicum lys*C gene which has been modified in any way to encode an aspartate kinase which is resistant to inhibition by lysine and/or threonine. The examiner further asserted that while the specification discloses overexpression by increasing the copy number of the gene of interest, there is no teaching as to which modifications in the promoter, regulatory region or the ribosome binding site of the recited genes will result in increased expression of the *lys*C gene. The examiner further alleged that the specification fails to disclose the structural modifications in the *C. glutamicum lys*C gene which are associated with resistance to inhibition by lysine and/or

threonine nor does it provide the structure of the mutant *C. glutamicum lys*C gene referred to in the specification as disclosed in EP-B-0 387 527.

The issue of enablement involves the question of whether an application enables one of ordinary skill in the art to make and to use the claimed invention. Clearly, the specification teaches that **increasing the encoded product (overexpression) of the *pyc*, *dap*A, and *lys*C genes increases L-lysine production**. This end result is described in clear and concise terms in the examples. The term "overexpression" is defined as a specific molecular manipulation by means of either increasing the copy number (*e.g.*, Example 6), enhancing the promoter activity (Examples 15-19, pg. 8, lines 27-31), or enhancing the regulatory region of the ribosome binding site located upstream of the gene of interest (pg. 7, lines 26-pg. 8, lines 9). Therefore, it is the applicants' position that increasing the L-lysine production in *C. glutamicum* by "overexpression" must be accomplished either by increasing the copy number, enhance the promoter, or increase the regulatory region of the ribosome binding site of the gene of interest.

Undue experimentation would not be required to increase L-lysine production by either enhancing the promoter or ribosome binding sites of the *lys*C, *pyc*, or *dap*A genes. Claims 27, 28, 31, and 32 satisfy the "how to make" prong of the enablement requirement because the scope of the claims are "reasonably correlated" with the teachings of the application [See MPEP §2164.01(b)]. The present specification (as originally filed) and ordinary skill in the art permit one to identify the promoter regions of the *lys*C, *dap*A (Examples 15-19), and the *pyc* gene, and mutate them to enhance activity (pg. 8, lines 27-31, Example 15). The teachings also fully enable one of skill to mutate the ribosome binding sites of the *lys*C, *dap*A, and *pyc* genes in order to stabilize the RNA for more efficient translation (see pg. 7, lines 26-pg. 8, line 23). Specifically, the sequences of the *lys*C, *dap*A, and *pyc* genes' regulatory regions and the means of mutating these regions is either well known in the art or disclosed by the present specification (pg. 8, lines 27-31; Example 3). Finally, each molecular manipulation of either increasing the copy number or enhancing the promoter or ribosome binding site can be easily assayed for via measurement of L-lysine production (see e.g., Example 12). Accordingly, due to the teachings of the specification and what was known in the art at the time of filing, the experimentation necessary to practice the present invention would not be undue.

As discussed above, however, solely for the purpose of expediting prosecution and without prejudice to the applicants' right to seek broader claims in a continuing application, claims 27 and 31 have been amended thereby obviating the rejection of these claims. In view of the foregoing amendments and remarks, the applicants respectfully submit that the rejection of claims 27, 28, 31, and 32 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement, has been overcome and should be withdrawn.

CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains at issue which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

Respectfully submitted,
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